

Impact of menopause on outcomes in prolactinomas after dopamine agonist treatment withdrawal

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Title

Impact of menopause on outcomes in prolactinomas after dopamine agonist treatment withdrawal

Short title

Impact of menopause on prolactinomas

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Summary

Objective: Discontinuation of dopamine agonist (DA) treatment in women with prolactinoma after menopause is a potential approach; studies systematically assessing long-term outcomes are lacking. Our aim was to investigate the natural history of prolactinoma in this group.

Design/Patients: Retrospective cohort study of women with prolactinoma diagnosed before menopause and who after menopause were not on DA.

Results: Thirty women were included. Twenty-eight received DA (median duration 18 years, median age at DA withdrawal 52 years). At last assessment (median follow-up 3 years) and compared with values 6-12 months after stopping DA, PRL increased in 15%, decreased but not normalized in 33% and was normal in 52%; PRL levels or visible adenoma on imaging before DA withdrawal, treatment duration and presence of macro-/microadenoma at diagnosis were not predictors of normoprolactinaemia at last review, whereas PRL values 6-12 months after stopping DA were. Adenoma regrowth was detected in 2/27 patients (7%), who showed gradual increase of PRL. Comparison with 28 women who had DA withdrawal before their menopause revealed lower risk of hyperprolactinaemia recurrence in the postmenopausal group (HR:0.316, 95% CI:0.101-0.985, $p<0.05$). Two women with microprolactinoma diagnosed in peri-menopausal period had not been offered DA; PRL decreased (but not normalized) during observation of 1 and 8 years.

Conclusions: PRL normalised over time in nearly half of the women and serum PRL 6-12 months after DA withdrawal is useful predictor. Nonetheless, 7% of the patients demonstrated adenoma regrowth which, given the life expectancy post-menopause, necessitate regular monitoring of the cases with persistent hyperprolactinaemia.

Keywords: Prolactinoma, menopause, dopamine agonists, prolactin

Introduction

Prolactinomas are the most common pituitary adenomas and are most frequently diagnosed in women of reproductive age (median 30.5-32 years)¹⁻³. Dopamine agonists (DA) are the first line treatment for patients with symptomatic tumours, aiming to lower prolactin (PRL), reduce adenoma size and restore gonadal function⁴. Established consensus on the optimal duration of DA therapy is lacking; the Endocrine Society USA suggests that treatment may be tapered and perhaps withdrawn in patients who have normal PRL and no evidence of tumour on MRI and have received DA treatment for at least two years⁴. Nevertheless, the probability of maintenance of remission is low with a meta-analysis showing persisting normoprolactinaemia after DA withdrawal in 21% of micro- and 16% of macroprolactinomas⁵; notably, the recurrences are most likely to occur within a year after stopping DA therapy^{6,7}.

The Endocrine Society USA guidelines also advise consideration of discontinuation of DA therapy in women with microprolactinoma when menopause occurs, with continuing surveillance⁴. This approach seems desirable, particularly given the issues relating with long-term compliance, costs and potential side effects of medical treatment. It should be noted, however, that the natural evolution of prolactinomas after menopause, a physiological state of oestrogen deficiency, has not been fully elucidated and there is indeed a scarcity of reports observing females with pre-existing prolactinoma beyond the menopause without continued use of DA therapy.

Experiments in rats have shown that oophorectomy results in reduction of the size and number of lactotrophs and of the intracellular abundance of PRL-secretory granules⁸ and that selective anti-oestrogen treatment inhibits lactotroph tumour growth in rats harbouring subcutaneously implanted PRL-secreting pituitary tumours⁹. Touraine *et al.*¹⁰ reported spontaneous reduction in PRL levels after menopause in four women with hyperprolactinaemia most likely attributed to prolactinoma. Karunkaran *et al.*¹¹ in a group of 11 females with microprolactinoma followed through menopause without DA treatment, reported normalization of PRL in 45% of them; however, the duration of follow-up and the outcomes of those who remained hyperprolactinaemic are not available. Therefore, studies systematically assessing this group of patients and providing long-term outcomes and

frequency of adenoma regrowth would be of value in clinical practice and would facilitate the establishment of optimal management protocols.

The aim of the present study was to investigate the natural history of prolactinoma in a series of women who have gone through menopause, who were no longer on DA therapy and were followed up in a large pituitary centre in the UK and to compare the risk of recurrence of hyperprolactinaemia of this group of patients with that of females with prolactinoma who had a trial of DA withdrawal before their menopause.

Patients and Methods

Patients

All women with the diagnosis of prolactinoma established before menopause and who after menopause were off DA treatment and were followed up in the Department of Endocrinology, Queen Elizabeth Hospital Birmingham, UK during the period between 2000 and 2017 were studied. As a control group, we used females with prolactinoma who discontinued DA treatment before menopause and were followed up in our Department during the same time period. The patients were identified through searches by the University Hospitals Birmingham IT Services in the electronic patient record, as well as through searching the Departmental database. The diagnosis of prolactinoma was based on the detection of hyperprolactinaemia (after excluding the presence of macroprolactin and potential secondary causes of high PRL) combined with evidence of an adenoma on pituitary imaging; **in patients offered DA therapy, it was further supported by tumour shrinkage during follow-up. Menopause was confirmed by permanent cessation of menstrual periods and elevated gonadotrophins.** Clinical, biochemical and imaging findings, medications at presentation and follow-up, and information on the outcomes of the patients were collected. The decision to stop DA treatment relied mainly on physician's and/or patient's preference. Serum PRL was subsequently checked at regular intervals and pituitary imaging was performed if PRL values showed gradual increase.

The study was completely retrospective in nature and involved no intervention beyond routine patient care. It was registered with and approved as an audit by the University Hospitals Birmingham NHS Foundation Trust.

Prolactin assay

Serum PRL was measured between 2000 and 2006 by a Bayer Advia Centaur immunometric assay (reference range for both assays: males 40-360 mIU/L; females 60-620 mIU/L), and between 2006-present by an E170 Roche Diagnostics immunometric assay (reference range: males 85-325 mIU/L; females 100-500 mIU/L). Both assays were standardised to IRP 84/500. PRL measurements with different assays or performed in different laboratories were not used in this study.

Statistics

Percentages were calculated for categorical data and medians with ranges for continuous variables. Cox regression analysis was used to assess the effect of various factors on achieving normal PRL in post-menopausal women and on recurrence of hyperprolactinaemia in the groups of patients; Hazard Ratios (HR) with 95% confidence intervals (CI) were estimated. The level of significance was set at $p<0.05$. Statistical analyses were performed by IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Results

Study population

i) Group of women who stopped DA treatment after menopause

We identified 50 women diagnosed with a prolactinoma before menopause and who had completed menopause before the time of last follow-up. A flowchart demonstrating the identification of the study population is shown in Figure 1. Amongst the patients from this original group, at last review, 16 were still on DA, whereas 34 were not on medical treatment. In the latter group, 4 patients had stopped the DA at least 8 years before menopause and were not included. For the remaining 30 women finally included, the median age at diagnosis of the prolactinoma was 34 years (range 16-49); two patients with microprolactinoma diagnosed in the peri-menopausal period had not been offered DA treatment and the remaining 28 (22 with micro- and 6 with macroadenoma) had received DA [median duration of treatment 18 years (range 3-34), 10 on bromocriptine (median dose 1.25 mg/day, range 1.25-5 mg/day) and 18 on cabergoline (median dose 0.5 mg/week, range 0.25-1 mg/week)] which had been stopped after menopause (at a median age of 52 years). In this group, 17/28 patients had visible adenoma on imaging before stopping DA. Median follow-up was 3 years (range 1-13) and was determined from the time of stopping the DA (or from the time of menopause in the two patients not offered DA) until the last serum PRL measurement.

ii) Group of women who stopped DA treatment before menopause

We identified 28 women with prolactinoma who had a trial of DA withdrawal before menopause. Their median age at diagnosis of the prolactinoma was 26 years (range 16-42), 23 had microadenoma and 5 macroadenoma, and they had received DA treatment for a median duration of 6 years (range 1-24; one of these patients had been on DA for one year and had chosen to stop it after achieving normal PRL) [5 on bromocriptine (median dose 2.5 mg/day, range 2.5-5 mg/day), 21 on cabergoline (median dose 0.25 mg/week, range 0.25-1 mg/week) and 2 initially on bromocriptine followed by cabergoline]. All had normal PRL and 14/25 had visible adenoma on imaging prior stopping DA. Median follow-up was 1 year (range 0.1-12 years) defined from the time of stopping DA until time of

detection of recurrence of hyperprolactinaemia or of last PRL measurement if this had remained normal.

Outcomes in women who stopped DA treatment after menopause

i) Post-menopausal changes in serum PRL levels

Prior to stopping the DA, serum PRL was normal in 16 and above the reference range in 12 patients (Table 1). Amongst those with normal PRL before stopping the DA, at their last review, PRL increased above the reference range in 5/16 (31%) and remained normal in 11/16 (69%). Of those with PRL above the reference range before stopping the DA, PRL had increased further in 8/12 (67%), decreased but did not normalize in 1/12 (8%), and normalized in 3/12 (25%) (Table 1). Overall, at last assessment of the total group, PRL demonstrated increase (with values above the reference range) in 13/28 (46%), decreased but did not normalize in 1/28 (4%), and was normal in 14/28 (50%) of the patients (Figure 2).

PRL checked between 6 and 12 months after stopping DA was normal in 9 and above the reference range in 19 patients (Table 2). Amongst those with normal PRL, PRL remained within normal limits in all, 9/9 (100%) at their last review. Of those with high PRL 6-12 months off DA, the last recorded review revealed that PRL had increased further in 4/18 (22%), decreased but did not normalize in 9/18 (50%) and normalized in 5/18 (28%) (Table 2). Overall, at last assessment of this group, PRL showed increase (with values above the reference range) in 4/27 (15%), decreased but did not normalize in 9/27 (33%) and was normal in 14/27 (52%) of the women (one patient was excluded from these evaluations because she restarted DA within one year after the rise of the PRL) (Figure 2). Details and outcomes of the 4 patients who had further increase in serum PRL after stopping DA therapy are shown in Table 3.

Univariate Cox regression analysis revealed that PRL levels or visible adenoma on imaging before stopping the DA, duration of treatment with DA, **type of DA, and size of the tumour at diagnosis (macro- or microadenoma)** were not predictors of having normal PRL at last assessment, whereas

PRL values within 6-12 months after stopping DA were (HR 0.996 per mU/L, 95% CI 0.004-0.999, $p<0.05$).

In the two patients with microprolactinoma diagnosed in the peri-menopausal period who had not been offered DA, serum PRL did not normalize, but decreased by 70% and 27% during observation periods of 1 and 8 years, respectively. In these patients, the lack of confirmation of prolactinoma diagnosis by demonstrating tumour shrinkage by DA treatment is a potential drawback; however, their basal PRL levels were 2920 and 1683 mU/L after having excluded secondary causes of hyperprolactinaemia.

In the total series of 30 patients, at last assessment 16 (53%) were hyperprolactinaemic.

ii) *Prolactinoma growth*

During the follow-up period, regrowth of the adenoma was detected in two patients (2/27, 7%) (Table 3). This was not associated with pressure effects. Both had microadenomas and had shown continuous gradual increase in their PRL levels (before stopping DA: 1893 and 2500 mU/L – at last review: 6121 and 4281 mU/L, respectively). After discussion with the patients, they were subsequently recommenced on DA.

Recurrence of hyperprolactinaemia after DA withdrawal: comparison between pre- and postmenopausal women

In the group of premenopausal women, 8/28 (29%) remained normoprolactinaemic and 20/28 (71%) had recurrence of hyperprolactinaemia at a median interval of 0.7 years (range 0.1-4.2) after DA withdrawal.

Using this group of patients and the post-menopausal females with normal PRL prior stopping DA in a Cox Regression model, it was found that after adjusting for size of the tumour at diagnosis (macro- or microadenoma), visible adenoma on imaging before stopping the DA and duration of treatment with DA, recurrence of hyperprolactinaemia was lower in the post-menopausal group (HR 0.316, 95% CI 0.101-0.985, $p<0.05$).

Discussion

This is the first series systematically reviewing the outcomes of females with prolactinoma who after reaching menopause had their DA treatment actively withdrawn. We found that during a median follow-up period of 3 years, 53% of the total patients had hyperprolactinaemia. In those previously treated with DA, this rate was 50%, with serum PRL within 6-12 months after stopping treatment being the only independent predictor. Interestingly, in 15% of the women, PRL showed an increase as compared to the levels measured between 6 and 12 months after DA withdrawal and two of these patients had adenoma regrowth. Our results suggest that despite the concept that menopause facilitates the remission of hyperprolactinaemia in women with prolactinoma, progress of the tumour is possible, as seen in 2 of our 30 patients, necessitating regular monitoring.

Previous published literature on this topic is very limited and has not elucidated the behaviour of the prolactinoma in the long term. Thus, Karunkaran *et al.*¹¹ in a retrospective study of 11 females with microprolactinoma diagnosed before and followed through menopause, reported that in five of them PRL normalised after the cessation of menses; in this group, only two had been previously treated with DA. It should be noted, however, that information on the time of assessment of PRL in relation to menopause, data on the outcomes of those who remained hyperprolactinaemic, and the duration of follow-up after the cessation of menses were not provided. Touraine *et al.*¹⁰ reported that in a small group of four females with hyperprolactinaemia most likely attributed to prolactinoma who did not receive any treatment once menopause was diagnosed, PRL levels decreased spontaneously in all [at onset of menopause: median 39.8 ng/ml (range 19-110) – during menopause: median 33.0 ng/ml (range 3-90)] during follow-up ranging between 66 and 155 months.

In our study, the outcomes of women who had actively withdrawn DA treatment before or after menopause and were followed-up during the same time period in our Department were compared. Given that all premenopausal women had normal PRL prior stopping DA, the comparison was performed with the group of postmenopausal females who before DA withdrawal had also normal PRL. We found recurrence of hyperprolactinaemia in 31% of the postmenopausal and in 71% of the premenopausal group. After adjusting for possible confounding factors including size of adenoma at

diagnosis, duration of DA treatment and visible adenoma on imaging prior DA withdrawal, we found that the risk of hyperprolactinaemia recurrence was lower in the postmenopausal group suggesting a favourable impact of menopause. Similar data comparing directly these two groups of women are not available and the published literature on DA withdrawal outcomes involves patients of both sexes and of any age. Thus, in a meta-analysis of studies including mainly females before menopause, the rates of persisting normoprolactinaemia after withdrawal of DA were only 21% (95% CI, 10-37%) for micro- and 16% (95% CI, 6-36%) for macroprolactinomas, with longer DA treatment duration associated with treatment success⁵. In a meta-analysis of reports including only patients treated with cabergoline, most of which were premenopausal females, the hyperprolactinaemia recurrence rate was 65% (95% CI 55-74%)¹².

In comparison with the PRL values detected between 6 and 12 months after DA withdrawal, PRL decreased but remained elevated above the reference range in 33% and normalised in 52% of our patients. Although this may reflect the natural course of the tumour or the cytotoxic effect of the previous DA treatment¹³, the reduction of oestrogen levels following menopause could also relate to this observation. In fact, experimental data on rats have shown that ovariectomy has a dramatic effect on the lactotroph cells with a decrease in their size and number, as well as a reduction in the intracellular abundance of PRL secretory granules; oestradiol is the dominant ovarian hormone that reverses these effects and subsequently stimulates PRL secretion⁸. We also found that PRL values within 6-12 months after stopping the DA were the only predictors of tumour secretory dynamics and normoprolactinaemia at last assessment providing guidance on the intensity of future surveillance and the selection of cases for possible discharge to primary care. Notably, in studies looking at predictive factors of persisting normoprolactinaemia after DA withdrawal, tumour remnant prior to DA withdrawal, longer duration of DA treatment and nadir PRL during treatment were the most commonly reported^{5-7,14}; however, these data were derived from patient groups comprising both men and women and a wide range of ages.

Interestingly, at last assessment and, in comparison with the PRL levels detected 6-12 months after stopping DA treatment, PRL showed increase (with values above the reference range) in 4/27 (15%)

of the patients (all had microadenomas at diagnosis). It is of note, that this was observed in women with high PRL levels (>2500 mU/L) measured 6-12 months after DA withdrawal (range of PRL of this group in our series 2633-4270 mU/L). During the follow-up period, regrowth of the adenoma was detected in two of them (7% of the total group), four and six years, after stopping the DA. Whether the rate of adenoma regrowth would be higher if our series included more macroprolactinomas or if the follow-up was longer remains a possibility. These findings demonstrate that the growth potential of the prolactinomas remains even after menopause. In accord with this is the observation that 94% of the prolactinomas diagnosed after menopause are macroadenomas¹⁵. Furthermore, the long interval until detection of tumour regrowth signifies the importance of prolonged monitoring in cases with persistent hyperprolactinaemia.

It has been previously shown that the PRL levels correlate with inflammatory biomarkers¹⁶ and that patients with untreated prolactinoma have metabolic disorders (including insulin resistance and dyslipidaemia) and an adverse cardiovascular risk profile¹⁷⁻²⁰. The significance of these findings and their potential consequences for the group of post-menopausal women with hyperprolactinaemia after DA withdrawal remain to be clarified.

A drawback of our study is the potential selection bias related to the decision on cessation DA treatment. A prospective series of non-selected, consecutive patients, who after menopause stop their DA therapy, could overcome this problem, but such a study may not be practically feasible. Furthermore, pituitary imaging was performed only in patients with gradual increase of serum PRL after treatment withdrawal. Nonetheless, given that in most of the cases PRL serves as a good marker of tumour behaviour²¹, it is unlikely that patients with adenoma regrowth may have been missed. Advantages of our study are the inclusion of subjects with systematic follow-up in the era of MRI with PRL measurements in a single laboratory (including routine macroprolactin screening) during the monitoring after DA withdrawal, and the use of a comparison group of females who stopped DA treatment before their menopause.

In conclusion, serum PRL normalises over time in nearly half of the women with prolactinoma who pass through menopause and are not on DA treatment; serum PRL 6-12 months after DA withdrawal

is a useful predictor for this and can guide clinical practice. The risk of recurrence of hyperprolactinaemia is lower in this group compared with premenopausal women who had a trial of DA withdrawal. Nonetheless, menopause is not a sufficient condition to ensure remission of the tumour; during our follow-up period, 7% of the total group demonstrated adenoma regrowth which, given the long life expectancy after menopause, necessitates regular monitoring of the cases with persistent hyperprolactinaemia. The potential long-term consequences of the untreated hyperprolactinaemia and studies with longer follow-up on this group of patients will provide further insights on the field.

Conflict of interest

Nothing to declare

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Table 1. Details and outcomes of patients who stopped dopamine agonist (DA) treatment.

Hyperprolactinaemia just before stopping DA			
	PRL higher at last follow-up	PRL lower but not normal at last follow-up	PRL normal at last follow-up
n=12* PRL (median, range) 1193 mU/L (603-2500) Adenoma visible on imaging before stopping DA n=9/12	n=8/12** (67%) PRL (median, range) 2644 mU/L (1000-6121) Adenoma visible on imaging before stopping DA n=6/8	n=1/12 (8%) PRL 550 mU/L Adenoma visible on imaging before stopping DA n=0/1	n=3/12 (25%) Adenoma visible on imaging before stopping DA n=3/3
PRL normal just before stopping DA			
	Hyperprolactinaemia at last follow-up		PRL normal at last follow-up
n=16 Adenoma visible on imaging before stopping DA n=8/16	n=5/16 (31%) PRL (median, range) 1025 mU/L (806-1088) Adenoma visible on imaging before stopping DA n=2/5		n=11/16 (69%) Adenoma visible on imaging before stopping DA n=6/11

*In this group: one patient was on citalopram (PRL 1893 mU/L); one patient on oestrogen treatment and on amitriptyline (PRL 1057 mU/L); one patient had compliance issues.

**One patient on amitriptyline (PRL 5622 mU/L) on which she was also even before stopping the DA.

As imaging before stopping the DA was used the available one closest to the time of cessation of the DA treatment (median interval 1 year).

Table 2. Details and outcomes of patients based on PRL levels 6-12 months after stopping dopamine agonist (DA) treatment.

Hyperprolactinaemia within 6-12 months after stopping DA			
	PRL higher at last follow-up	PRL lower but not normal at last follow-up	PRL normal at last follow-up
n=19 [^] PRL (median, range) 908 mU/L (680-4270) Adenoma visible on imaging before stopping DA n=10/19	n=4/18* [^] (22%) PRL (median, range) 4957 mU/L (3440-6121) Adenoma visible on imaging before stopping DA n=2/4	n=9/18* (50%) PRL (median, range) 1046 mU/L (550-1848) Adenoma visible on imaging before stopping DA n=5/9	n=5/18* (28%) Adenoma visible on imaging before stopping DA n=3/5
Normal PRL within 6-12 months after stopping DA			
	Hyperprolactinaemia at last follow-up		PRL normal at last follow-up
n=9 Adenoma visible on imaging before stopping DA n=7/9	-		n=9/9 (100%) Adenoma visible on imaging before stopping DA n=7/9

*One patient was excluded because she restarted DA shortly after the first PRL measurement.

[^] One patient on amitriptyline (PRL 5622 mU/L) on which she was also even before stopping the DA treatment.

Table 3. Details and outcomes of the patients who had further increase in the PRL values compared with those detected 6-12 months after stopping dopamine agonist (DA) treatment.

Patient	PRL within 6-12 months after stopping DA (mU/L)	PRL at last follow-up (mU/L)	Adenoma size at diagnosis	Residual adenoma on MRI before stopping DA	Follow-up after stopping DA (years)	Findings of latest pituitary MRI	Outcome
1	4270	6121	Microadenoma	Yes	6	Increase in size (of around 2 mm) of residual adenoma	Restarted cabergoline with PRL gradually decreasing – repeat MRI showed reduction in adenoma size
2	3280	3440	Microadenoma	No	4	No MRI given the no substantial increase of PRL values	Under surveillance
3*	3149	5622	Microadenoma	Yes	6	Stable appearances of the residual adenoma	Under surveillance
4	2633	4281	Microadenoma	No	4	Regrowth of the adenoma (measuring around 4 mm)	Restarted cabergoline – PRL decreasing - awaits pituitary MRI

*On stable dose of amitriptyline during all follow-up period.

Figure legends

Figure 1: Flowchart showing the identification of the study population. The characterisation of the tumour as micro- or macroadenoma relied at time of prolactinoma diagnosis. DA: dopamine agonist.

Figure 2. Serum PRL values for each individual patient just before stopping dopamine agonist (DA) treatment, within 1 year after stopping DA and at last assessment: (A) Patients with microprolactinoma at diagnosis, (B) Patients with macroprolactinoma at diagnosis. The values of last measurement are also shown at the top of the relevant column.